REMARKS

Alleged rejections under 35 U.S.C. §102(b)

Claims 4, 9, 14 and 23 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Chiang et al., J. of Clin. Endo. & Metabolism 2000; 85(10): 3828-3839. It is asserted that Chiang teaches a method of modulating senescent human cells by administering an effective amount of an inhibitor of adenylate cyclase, protein kinase A, and protein kinase C.

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation has been presented. Reconsideration and withdrawal of this rejection is requested.

Applicants respectfully point out that the Chiang document does not report a method that "modulates cellular senescence in the patient." Chiang et al. report on attempts to regulate estrogen receptor (ER) expression with human chorionic gonadotropin (hCG) and gonadotropin releasing hormone (GnRH). Chiang et al. also assert that progesterone expression can be regulated through the regulation of ER. The focus of the Chiang document is therefore on hormonal regulation of ER, and not on cellular senescence. Indeed, there is no mention or discussion on aging or cellular aging anywhere in the document. The Chiang document for this reason alone does not anticipate the present inventions because the document does not disclose, teach or report the modulation of cellular senescence.

The present rejection is also misplaced because the Chiang document does not report the administration of an "effective amount" of inhibitor. The inhibitors in the Chiang document were used to study the regulation of ER levels by hCG and GnRH in connection with the PKA or PKC pathways in hGLCs. In order to do so, the hGLCs were *pretreated* with inhibitors. *See* Chiang et al., p. 3831, col. 2, first full paragraph. Subsequently, the hGLCs were treated with hCG or GnRH, hCG or GNRH in conjunction with an inhibitor, and with the inhibitors. *See* Chiang et al., pp. 3833-3835 and Figures 6-7. Chiang et al. report that (1) hCG and GnRH had a down-regulating effect; (2) this effect was reduced in the presence of the inhibitors; and (3) the inhibitors alone had no effect at all. *See id.* There is no discussion whatsoever of what might constitute an "effective amount" of inhibitor because the study was focused on the effects of hCG and GnRH, and the hGLCs in the presence of the inhibitors presented a baseline against

which the effect of hCG and GnRH were measured. This conclusion is supported by the fact that the amount of inhibitor administered did not vary (see Figures 6 and 7).

Finally, the present rejection is misplaced at least with respect to claims 9 and 14 because the hGLCs reported by Chiang et al. are not "senescent" cells. Chiang et al. report the use of hGLCs that were obtained by subculturing cells separated from the follicular fluid of *in vitro* fertilization participants. Chiang et al., p. 3829, col. 2. The hGLCs were therefore already treated while *in vivo* with hormones such as hCG and GnRH, and were consequently may already have been in a down-regulated state. *Id.* at p. 3837, col.1. The hGLCs reported by Chiang et al. were therefore not aging cells that had reached a senescent state. Moreover, the pretreatment of the cells *in vivo* may have already altered the state of the cell. For these reasons, the use of the hGLCs reported by Chiang et al. makes analogy of the study of ER expression in that document to modulation of aging cells suspect, if not impossible.

In conclusion, the Chiang document does not anticipate the present inventions at least because it reports on the regulation of ER expression and not on the modulation of cellular senescence. In addition, the document does not report the effective amount of inhibitor required to modulate cellular senescence, nor does it report on the modulation of senescent cells due to the nature of the hGLCs used by Chiang et al. In light of the above, Applicants respectfully request reconsideration and withdrawal of the anticipation rejections.

Alleged rejections under 35 U.S.C. §103(a)

Claims 4, 6, 8-15 and 23-27 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Chiang et al. (cited above) in view of Chaves et al., Gerontology 2002; 48: 354-359. Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of obviousness has been presented. Reconsideration and withdrawal of this rejection is requested.

As discussed above, the Chiang document does not anticipate claims 4, 9, 14 and 23 and its dependent claims because at a minimum Chiang et al. do not report the modulation of cellular senescence, or cellular aging, and because the Chiang document does not report the use of an "effective amount" of inhibitor for modulation of cellular senescence. The present rejection for obviousness is misplaced because Chaves et al. do not remedy the defects of the Chiang document.

The Chaves document does not remedy the defects of the Chiang document because Chaves does not report "a correlation between a protein kinase C inhibitor and aging." Contrary to the assertion of the Office Action, Chaves concludes that the data "suggest that the inhibition of PKC induced an *age-dependent* blockade of the ROS generation." *See* Chaves et al., p. 358, col. 2, second full paragraph (emphasis added). It should be noted that this conclusion is tenuous at best, since the results demonstrated no statistical difference ($p>0.05$) in relation to the inhibition percentage of ROS production by the PKC inhibitor. *See* Chaves et al., p. 358, col. 1, third full paragraph and Table 3.

In any event, the conclusion reached by Chaves et al. regarding the "*age-dependent*" inhibition only means that there is a correlation between PKC activity and *the age of the subject.* This is entirely different from a correlation between PKC activity and *the aging mechanisms of the cells*. In fact, no such correlation is between PKC activity and cellular senescence is reported by Chaves et al.

Chaves et al. reported the study of the amount of reactive oxygen species (ROS) generated by granulocytes separated from venous blood of subjects that had been divided into age groups. The amount of ROS production was measured after treatment of the cells with phorbol 12, 13-dibutyrate (PDB), a PKC activator. PKC inhibitor was used in two ways: first, the PKC inhibitor was used to establish a dose-response curve, and second, PKC inhibitor was added to cells that had been pretreated with PDB. Thus the PKC inhibitor was not used in relation to the regulation of cellular senescence or to correlate PKC and aging, but instead was used to study the regulation of the amount of ROS production by PDB.

Furthermore, characterizing the effect of PKC in the Chaves document as an indicator of modulation of cellular senescence would be misplaced. Chaves et al. induced ROS production with PDB, which is not a natural PKC activator. It is plain that adding PKC inhibitor to cells that had been artificially pretreated with PDB, a known PKC activator would result in some effect, but this effect on the PDB-pretreated cells cannot and should not be equated with modulation of cellular senescence.

For all of the above reasons, no *prima facie* case of obviousness has been established because at a minimum the documents do not report every feature of the rejected claims, contrary to the well-settled standard in U.S. patent law that all claim features must be taught or suggested (see MPEP 2143.03 and the case decisions cited therein).

Moreover, no rationale has been presented as to how a person of ordinary skill in the art would reasonably expect success in combining the references. Chiang et al. report the use of an inhibitor in the study the effect of hCG and GnRH on ER expression and regulation. Chaves et al. report on the use of an inhibitor in the study of the effect of PDB on ROS production in cells of subjects from different age groups. Therefore, a combination does not teach the modulation of cellular senescence by inhibitors, but instead would only result in the study of ER expression and regulation of cells from subjects in different age groups. No articulation of how this combination would result in the modulation of cellular aging mechanisms has been presented.

Furthermore, with respect to claims 6, 8, 10-13, 15 and 24-27, the Office Action uses improper hindsight to assert that the choice of particular types of human cells and particular compounds would have been obvious. The standards for a *prima facie* case of obviousness require that some basis for the selections in the claimed inventions. The present Office Action, however, has not articulated any reasons why such selections would be made, and consequently constitutes improper hindsight.

For all of the above reasons, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections.

Conclusion

It is believed that the application is now in condition for allowance. Applicants urge the Examiner to pass the application to issue.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at the number provided below.

The Commissioner is hereby authorized to charge JHK Law's Deposit Account No. **502486** for such fees required under 37 CFR §§ 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486**.

DATE: March 26, 2008

Respectfully submitted,

/Joseph Hyosuk Kim/
Joseph Hyosuk Kim, Ph. D.
Registration No. 41,425

JHK Law
P.O. Box 1078
La Canada, CA 91012-1078
Telephone: 818-249-8177
Facsimile: 818-249-8277